REMARKS

Rejection of the claims under 35 USC § 112

Claims 14 and 18 have been rejected under 35 U.S.C. 112, second paragraph, as being indefinite for depending from canceled claims. Applicants have amended the claims to obviate the rejection.

Rejection of the claims under 35 USC § 103

Claims 11 and 13-18 have been rejected under 35 U.S. C. 103 as being unpatentable over Zimmer (Methods, 1999) in view of Vaish et al (NAR 1998). Applicants respectfully disagree.

The action states, on page 3, that the instant specification does not define the term "target tissue". However, the claim clearly states that the solution is injected into an efferent or afferent vessel of the target tissue. Therefore, the tissue can not be *any* tissue, as interpreted in the action. The target tissue must be a tissue for which the injected vessel an afferent or efferent vessel. The terms afferent vessel and efferent vessel are defined in the specification on page 3 lines 26-31, this definition being the ordinary and customary meaning of the term in the art.

The action notes that Zimmer et al. injected RNA-containing particles into the tail vein of mice and observed delivery to liver. However, Zimmer et al. did not teach "wherein the volume of the solution and the rate at which the solution is injected increases the volume of fluid within a vessel in the target tissue resulting in increased hydrostatic pressure against a wall of the vessel thereby increasing permeability of vessel and delivering the double strand RNA oligonucleotide from inside the vessel, through the wall of the vessel, into the extravascular space and into the in vivo parenchymal cell." Zimmer et al. injected 5nmol/5ml/kg into the tail vein of mice. Given a weight typical of a mouse of 25 g, this corresponds to an injection volume or 125 μl (25g/mouse × 5 ml/1 kg ×1 kg/1000 g = 0.125 ml/mouse = 125 μl/mouse). Applicants have previously filed a declaration under 37 CFR 1.132 showing that injection of this volume would fail to increase hydrostatic pressure against a wall of the vessel thereby increasing permeability of vessel.

The action states, on page 7, that the Examiner is of the opinion that the pressure against the vessel walls would inherently be increased, in the method of Zimmer et al., because the needle used to deliver to oligonucleotide is external to the tail vein. However, the Applicants' claims clearly recite that it is the solution which results in pressure against a wall of the vessel. Merriam-Webster defines hydrostatic as "of or relating to *fluids* at rest or to the pressures they exert or transmit" (italics added). This definition is in agreement with the Applicants' usage of the term.

In the present office action, the Examiner states "Therefore, Applicants' Declaration under 37 C.F.R. § 1.131 is sufficient enough to overcome the prior art reference of Zhang et al. (Human Gene Therapy, 1999) but not sufficient enough to overcome the prior art reference of Zimmer (Methods, 1999).

Applicants' note that the Examiner has previously stated (Office Action dated 03/21/2008): "Specifically, the Examiner has found the results contained within the Declaration filed under 37 C.F.R. s1.132 at page 4 to be persuasive. It is formally agreed that the injection volume of 125 μl, taught by Zimmer et al. would not be enough to cause an increase in hydrostatic pressure sufficient to cause an increase in vascular permeability within the vessel as recited in the instant claims." (page 4, first full paragraph) and "The Examiner acknowledges that Zimmer et al. do not teach Applicant's claimed limitation that the volume of solution and the rate at which the solution is injected increases the volume of fluid within a vessel in the target tissue resulting in increased hydrostatic pressure against a wall of the vessel thereby increasing permeability of the vessel is increased sufficient to cause an increase in vascular permeability within the vessel." (page 5 first paragraph).

The Examiner's rejections are now believed to be overcome by this response to the Office Action. In view of Applicants' arguments, it is submitted that claims 11, 14-16 and 18 should be allowable.

Respectfully submitted,

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I hereby certify that this correspondence is being transmitted to the USPTO on this date: 03/19/2009 .

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